REMARKS

Claims 13, 14, 16-21, 31, 32, and 43-50 are pending in the instant application. By this amendment, claims 13, 21, 43-47, and 49 have been amended and new claims 51-54 have been added. Support for the amendments to claims 13 and 21 can be found in paragraph [0038] of the specification as filed. Claims 43-47 and 49 have been amended to incorporate their proper dependency. Support for the amendment to claims 43 and 44 can be found in paragraphs [00200]-[00211] of the specification as filed. Support for the amendment to claims 45-47 and 49 can be found in paragraphs [00159]-[00174] of the specification as filed. Support for new claims 51-54 can be found in paragraph [0037] of the specification as filed. Thus, all amendments and new claims are fully supported by the application as originally filed and, as such, do not constitute new matter. Therefore, upon entry of this Amendment, claims 13, 14, 16-21, 31, 32, and 43-54 will be pending. Applicants request consideration and entry of the amendments and remarks into the record.

I. The Rejections For Lack Of Enablement Should Be Withdrawn

The Examiner has maintained the rejection of claims 13, 14, 16-21, 31, 32, and 43-50 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. It is the Examiner's contention that although the specification is enabling for a method of using a tissue protective cytokine receptor complex comprising an EPO receptor (EPO-R) and/or a βc receptor in screening assays to identify a compound that exhibits a tissue protective activity, the specification does not provide enablement for a method of using any other tissue protective cytokine receptor complexes in screening assays to identify a compound that exhibits a tissue protective activity. In accordance with the Examiner's suggestion, the claims have been amended to recite a tissue protective cytokine receptor complex comprising an erythropoietin receptor and a βc receptor. In view of this amendment, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, be withdrawn.

II. The Rejections For Indefiniteness Should Be Withdrawn

Claims 13, 14, 16-20, 31, 32, and 43-50 are rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that claim 13, and its dependent claims, are indefinite because they recite "assaying the identified test

compound for a tissue protective activity" but allegedly fail to point out how to assay the test compound for a tissue protective activity and what tissue protective activity is determined.

Applicants submit that the term "tissue protective activity" is clearly defined in the specification. At page 13, paragraph [0037] of the specification as filed, "tissue protective activity" is defined as "the effect of inhibiting or delaying damage or death of a cell, tissue, or organ." Moreover, the specification is replete with methods by which the tissue protective activity, *i.e.*, the effect of inhibiting or delaying damage or death of a cell, tissue, or organ, of the identified compound, can be assayed. Indeed, Section 5.3 at page 53 of the specification, entitled "Assays for Identifying Compounds or Testing Compounds Identified in Screening Assays," provides a multitude of assays to be used in accordance with the invention. Such assays incorporate both *in vitro* and *in vivo* methods and include: 1) biological screens (*see* Section 5.3.1 at page 53); 2) cell binding assays (*see* Section 5.3.2 at page 55); 3) cytokine and cell proliferation/differentiation assays (*see* Section 5.3.3 at page 57); 4) assays employing fusion proteins (*see* Section 5.3.4 at page 58); and 5) assays employing animal models (*see* Section 5.3.5.1 at page 60). Given this disclosure, one of skill in the art would clearly understand how to assay a given test compound for tissue protective activity.

With respect to the newly added claims, claims 51- 54 more particularly define the tissue protective activity being assayed. In particular, claim 51 requires that the tissue protective activity inhibits damage of a cell, tissue, or organ; claim 52 requires that the tissue protective activity inhibits death of a cell, tissue, or organ; claim 53 requires that the tissue protective activity is specific to excitable cells, tissues, or organs, and claim 54 requires that the tissue protective activity is specific to excitable cells, tissues, or organs of the central nervous system.

For all the reasons discussed above, Applicants believe that claim 13, 14, 16-20, 31, 32, and 43-50, as well as new claims 51–54, are clear and definite. Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, for indefiniteness, be withdrawn.

III. The Rejections For Obviousness Should Be Withdrawn

Claims 13, 14, 17, 19, 20, 48, and 49 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jubinsky, *et al.* (Blood 90:1867-1873, 1997, "Jubinsky") in view of Mercury™ Pathway Profiling System User Manual (Clontech, March 2, 2001, "Mercury"). The Examiner alleges that: (i) Jubinsky teaches a functional complex comprising the EPO

receptor (EPO-R) and a βc receptor in murine Ba/F3 cells that were transfected with either the murine EPO-R or EPO-R/βc, a functional role for the βc receptor in the EPO-dependent proliferation of Ba/F3 cells expressing the EPO-R, and a method for identifying the effect of sense, antisense, and nonsense oligodeoxynucleotides to βc on EPO-dependent proliferation and β-globin expression in Ba/F3 cells; and (ii) Mercury teaches various reporter genes and vectors containing a promoter and response element which control the transcription of the reporter genes and an assay for screening a compound for its effect based upon the reporter gene activity. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Jubinsky to include the reporter system of Mercury with a reasonable expectation of success, and motivated to do so because the Mercury system is ideal for use with membrane receptors.

The Examiner has further maintained the rejection of claims 13, 16-18, 21, 43-48, and 50 under 35 U.S.C. § 103(a) as being unpatentable over Jubinsky in view of Trueheart *et al.* (U.S. Patent No: 6,159,705, December 12, 2000, "Trueheart"). The Examiner concluded that Trueheart teaches rapid, reliable, and effective assays for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a heterologous receptor and that the cells used in the assays provided by Trueheart may be of prokaryotic or eukaryotic origin and may include yeast cells. The Examiner asserts that it would have been obvious to one having skill in the art to combine the method of Jubinsky to functionally express the EPO-R and βc receptor in a prokaryotic cell, such as a yeast cell or a human cell, in order to screen various compounds using a reporter gene taught by Trueheart, in order to identify a compound that modulates a tissue protective productive activity of the EPO-R/βc receptor complex with a reasonable expectation of success. The Examiner contends that one would have been motivated to do so because the assay system of Trueheart provides a rapid, reliable, and effective assay for screening and identifying effectors of a receptor protein or complex thereof.

For the reasons set forth below, Applicants disagree, and request the Examiner's reconsideration of the rejection of claims 13, 14, 16-21, and 43-50 for obviousness over Jubinsky in view of Mercury or in view of Trueheart.

A. The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have

been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a).

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467. The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Finally, evidence of unexpected or unobvious results is objective evidence of nonobviousness, and may be used to rebut a *prima facie* case of obviousness. *In re Wagner*, 371 F.2d 877 (C.C.P.A. 1967); M.P.E.P. § 716.02.

B. The Claimed Invention is Nonobvious over Jubinsky Combined With Mercury Or Trueheart

Applicants assert that, given the state of the art at the time of filing the application, the invention claimed in claims 13, 14, 16-19, 20, 21, and 43-50, as amended, and new claims 51-54, is nonobvious over the prior art. At the relevant time period, *i.e.*, the filing date of the instant application, September 30, 2003, one of skill in the art would not have been motivated to combine Jubinsky with either Mercury or Trueheart with the expectation of successfully arriving at the claimed method for identifying a compound with tissue protective activity.

1. The Prior Art

The obviousness inquiry properly begins with determination of the scope and content of the prior art. The Examiner states at page 6 of the Office Action that the claimed invention would have been obvious over Jubinsky (Jubinsky *et al.*, 1997, Blood 90: 1867-1873; "Jubinsky"), based on (1) Jubinsky's teaching that BaF3 cells expressing EPO Receptor and the common β chain (βc) required Epo for survival, and (2) Jubinsky's teaching that antisense ODN to β mRNA inhibits Epo-dependent proliferation of Ba/F3-Epo-R. This leads the Examiner to conclude that Jubinsky teaches a tissue protective role for a functional complex

comprising the EPO receptor and a common β chain (βc) in murine Ba/F3 cells (see Office Action, p. 6). However, this conclusion is contradicted by the prior art of record.

The Jubinsky experiments, published in 1997, did not suggest EpoR and βc formed a receptor complex that mediated tissue protective activity. Jubinsky may have suggested an interaction between βc and EPOR in Ba/F3 cells, and even that antisense to βc could inhibit Epo-dependent proliferation of Ba/F3 cells that expressed EPO-R. However, although Jubinsky optimistically interpreted these experiments to suggest "that βc functionally influences the EpoR proliferative signaling pathway" (at page 1871 col. 2), Jubinsky did not suggest EpoR and βc formed a receptor complex that mediated tissue protective activity. In fact, Jubinsky even conceded that its experiments "did not infer that βc is required for Epo-induced cell growth," but, rather, suggested that βc might act as an ancillary protein that "helps to stabilize or maintain an active [Epo] receptor complex" (Jubinsky, at page 1871, col. 2). Thus, Jubinsky teaches the use of the classical EPO receptor complex, possibly stabilized by βc, not a βc-EpoR complex.

Moreover, Jubinsky did *not* determine a necessary role for βc in the EPO-dependent survival. Jubinsky uses two cell types in their experiments: (i) Ba/F3 cells comprising EPO-R; and (ii) Ba/F3 cells comprising both EPO-R and βc. Jubinsky teaches that both of these cell types required EPO for survival (*see* Jubinsky at page 1868, stating "[b]oth Ba/F3p-EpoR and Ba/F3-EpoR + βc required EPO for survival...). As such, one of skill in the art could not make any conclusion concerning the role for βc, *per se*, in the EPO-dependent survival of the Ba/F3 cells.

Thus, Jubinsky failed to demonstrate any functional role for βc in the EpoR proliferative pathway *in vivo*. As discussed in Applicants' Amendment submitted on November 30, 2007, Jubinsky points out that "animals deficient in either βc or βIL-3 have not been reported to have impaired erythropoiesis." (Jubinsky at page 1872, citing to Nishinakamura, *et al.*, Immunity 2:211, 1995 ("Nishinakamura") and Stanley, *et al.*, Proc. Natl. Acad. Sci. 91:5592, 1994 ("Stanley")). Jubinsky attempted to provide a possible explanation for why both Nishinakamura and Stanley saw no change in responsiveness to EPO in animals that lack either βc or βIL-3 receptor genes by raising the possibility that EPO interacts with the non-disrupted β chain in these mice (Jubinsky, at page 1872). Jubinsky concluded "[t]herefore, mice deficient in *both* βc and βIL-3 will need to be assessed, as these two chains have functional redundancy. Such mice would be more analogous to our studies..." (*Id.*, emphasis added).

In 2000, several years after the Jubinsky publication, the interaction between βc and EpoR was reassessed in a paper published in the same journal that had originally published Jubinsky (*see* Scott *et al.*, Blood, 2000, 96: 1588-1590; cited as reference C39 in the Information Disclosure Statement filed on March 9, 2005; "Scott"). In the Scott study, mice lacking *both* the βc and βIL-3 receptor genes -- the very mice that Jubinsky had suggested should be studied -- were indeed produced. The result: no effect of βc on EPO responsiveness was detected in these mice (*see* Scott at page 1590). Scott concluded that the results of studies performed in cell lines, such as that of Jubinsky, did not have physiological significance (see Scott at page 1590). In discussing their findings as they relate to previous findings, including Jubinsky, Scott, at page 1590, states:

> [T]he demonstration of direct physical interaction involving the βc/βIL-3 receptor systems in cell lines did not extrapolate to an interaction of physiological significance in primary hematopoietic cells. This result is important for interpreting the significance of biochemical interactions between receptor molecules, particularly in studies in which cell lines are employed.

Thus, Scott suggests that the findings of Jubinsky lack significance because they could not be supported, and in fact they were disproved, by primary cell data.

Thus, by September 30, 2003, the time of the filing of the instant application and the relevant time period for a proper determination of obviousness, the prevailing view was that βc did *not* functionally interaction with the EPO receptor, and that any previous studies which purported to find such interactions between βc and the EPO receptor lacked functional significance.

2. The Claimed Invention Was Nonobvious Over The Prior Art At The Filing Date Of The Instant Invention

Against this background, the finding that EPO interacted with βc to form a functional receptor complex that mediated tissue protective activity was entirely unexpected. Given the teaching of Jubinsky and Scott, one of ordinary skill in the art at the time of filing of the instant application would not have believed that a functional association between EPO-R and βc existed either *in vivo* or in primary cell cultures. Indeed, first Jubinsky, and then Scott, clearly teach against such a conclusion. As noted above, even Jubinsky stated that one could not conclude from the study that βc is required for Epo-induced cell growth, and interpreted its results to merely suggest that βc might act as an stabilizing protein for the EpoR complex

(Jubinsky at page 1871 col. 2, "βc helps stabilize or maintain an active [EPO] receptor complex").

It was not until the Applicants' discovery that the hematological activity of EPO could be separated from its tissue protective activity described in the instant application, that the claimed methods for identifying compounds that modulate tissue protective activity using tissue protective complex comprising an EPO receptor and a βc receptor were imaginable. Applicants first found that a limited class of tissue protective cytokines modulate tissue protective activity through a receptor pathway that does *not* involve the classical EPO receptor dimer (*see, e.g.*, page 3, paragraphs [0006] and [0007] of the specification as filed). This alternative receptor was determined to be a heteromultimer receptor complex comprising EPO-R and the βc receptor which is found in excitable tissues such as the brain and spinal cord (*see, e.g.*, page 18, paragraph [0059] of the specification as filed). Applicants then successfully extrapolated their findings to primary cell cultures, demonstrating that cardiomyocytes isolated from βc (-/-) knock-out mice lack tissue protective activity in response to EPO, whereas cardiomyocytes from wild-type mice having intact βc chains were afforded the tissue protective effect of EPO (see Example 5 at page 106 of the specification as filed and Figure 7).

Therefore, one of ordinary skill in the art in 2003 would not have been motivated to combine Jubinsky with either of Trueheart or Mercury with any reasonable expectation of success of arriving at the invention as claimed in claims 13, 14, 16-19, 20, 21, and 43-50. Each of these claims require a cell expressing a tissue protective heterologous EpoR/ βc receptor complex, the existence of which was not known at that time. Moreover, because the prevailing belief at the time was that βc does <u>not</u> play a functional role in erythropoietic pathway in primary cells, one of skill in the art would have no motivation to combine the cells used in Jubinsky with either Trueheart or Mercury to search for a compound that modulates a tissue protective activity.

With respect to the newly added claims, claims 51- 54 are nonobvious over the prior art for the following additional reasons. Claim 51 requires that the assay in step (c) measures inhibition of damage of a cell, tissue, or organ. Nothing in Jubinsky, taken alone or combined with Mercury or Trueheart, suggests an assay that measures inhibition of damage to a cell, tissue, or organ. Claim 52 requires that the tissue protective activity inhibits the death of a cell, tissue, or organ, whereas neither Jubinsky, either alone or combined with Mercury or Trueheart, suggests such an assay. Claim 53 requires that the tissue protective

activity is specific to excitable cells, tissues, or organs; neither Jubinsky, either alone or combined with Mercury or Trueheart, suggest an assay for tissue protective activity in an excitable cell, tissue, or organ. Finally, claim 54 requires that the tissue protective activity is specific to excitable cells, tissues, or organs of the central nervous system, whereas neither Jubinsky, either alone or combined with Mercury or Trueheart suggest an assay for tissue protective activity in a cell, tissue, or organ of the central nervous system. Thus, new claims 51-54 are nonobvious over Jubinsky combined with Mercury or Trueheart.

In view of the arguments above, Applicants assert that it would not have been obvious to one of ordinary skill in the art to combine the teachings of Jubinsky with either Mercury or Trueheart to identify a compound that modulates a tissue protective activity of the EPO-R/βc complex. Therefore, Applicants respectfully request that the rejection of claims 13, 14, 16-19, 20, 21, and 43-50 under 35 U.S.C. § 103(a), for obviousness, be withdrawn.

CONCLUSION

Applicants respectfully request entry of the amendments and consideration of remarks above. Withdrawal of all the rejections and an allowance are earnestly sought.

Respectfully submitted,

Date: July 28, 2008

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